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Pathologic Characteristics of Digestive Tract and Liver in Patients with Coronavirus Disease 2019

Chunxiu Yang, PhD[a,1], Lijun Cai, MD[b,1], Shu-Yuan Xiao, MD[c,*]

KEYWORDS

• COVID-19 • Pathologic characteristics • SARS-CoV-2 • Lymphocytic infiltration

KEY POINTS

- The common digestive manifestations associated with coronavirus disease-2019 (COVID-19) include anorexia, nausea, vomiting, and diarrhea; the clearance of the viruses in COVID-19 patients with digestive symptoms is usually delayed.
- COVID-19-associated gastrointestinal histopathology is characterized by mucosal damage and lymphocytic infiltration.
- The most common hepatic changes are steatosis, mild lobular and portal inflammation, congestion/sinusoidal dilatation, lobular necrosis, and cholestasis.

INTRODUCTION

With the high prevalence of coronavirus disease-2019 (COVID-19), there has been increasing understanding of the pathologic changes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus can infect multiple organs and cause multiorgan symptoms, causing a wide range of clinical manifestations,[1] including respiratory, cardiovascular, gastrointestinal (GI), and neurologic symptoms (including loss of smell and taste),[2,3] as well as skin manifestations[4] (erythema and papules). A meta-analysis has shown that 17.6% of patients with COVID-19 have GI symptoms, and that viral RNA is detected in stool samples in 48.1% of patients.[5] Neglecting GI symptoms may sometimes delay a timely diagnosis

[a] Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [b] Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, China; [c] Department of Pathology, University of Chicago Medicine, University of Chicago Medicine, MC6101, Anatomic Pathology, 5841 South Maryland Avenue, Chicago, IL 60637, USA
[1] Co-first authors.
* Corresponding author.
E-mail address: Shu-Yuan.Xiao@uchospitals.edu

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and may permit the unchecked fecal-oral transmission of the virus. Ulcerative lesions occur in the GI tract in some patients, but only a few studies have described the histopathology of these lesions.[6] In addition, hepatic injury is a frequent complication of COVID-19 and is associated with the severity of the disease. Studies in patients with COVID-19 have shown the incidence of liver injury ranges from 14.8% to 62%, usually indicated by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels accompanied by slightly elevated bilirubin levels.[7–10] In fatal cases, the incidence of liver injury may reach up to 58% to 78%.[7] Pathologic findings in the GI tract and liver come mostly from autopsies or postmortem biopsies but may include pathologic examination of GI biopsies obtained premortem by GI endoscopy. This review summarizes the pathologic changes in the digestive system and liver associated with COVID-19, including the injuries induced by SARS-CoV2 infection of GI epithelial cells and the systemic immune responses.

Esophageal Pathology

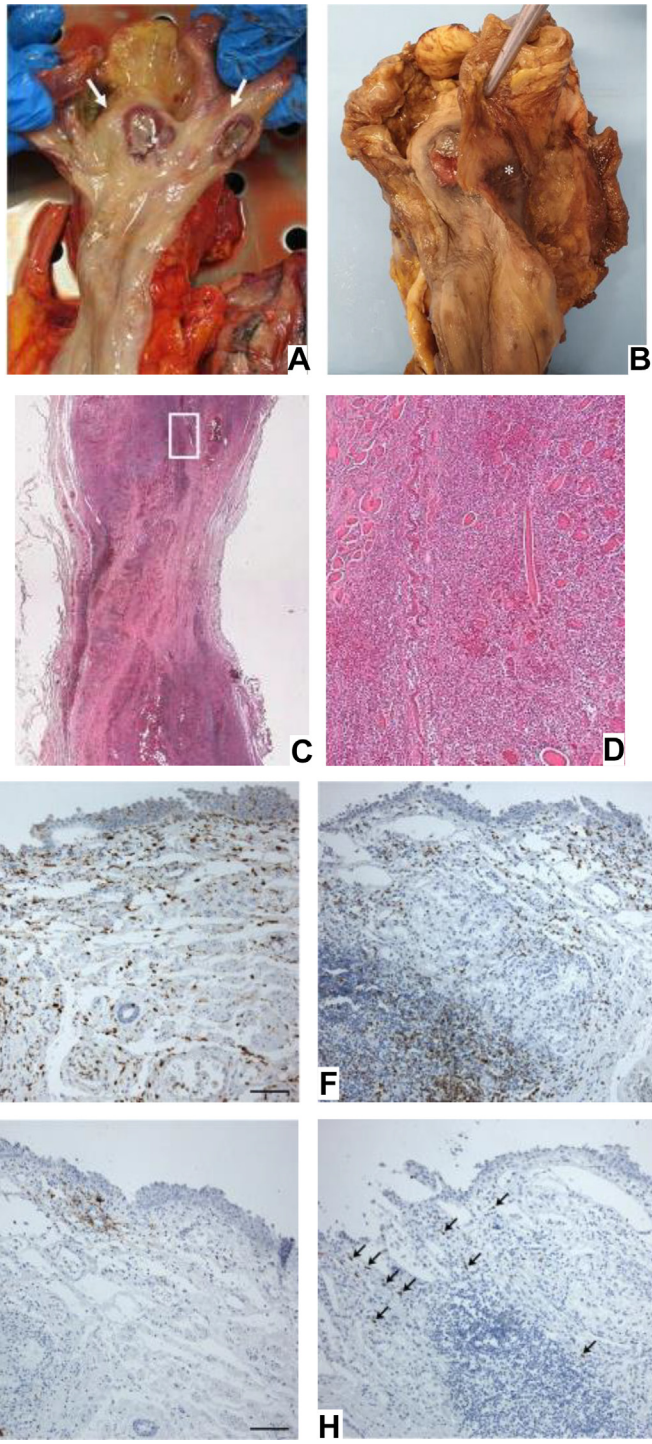
Although the clinical manifestations of COVID-19 are usually dominated by respiratory symptoms, some patients may lack symptoms and imaging features of COVID-19 pneumonia but only show GI symptoms.[11] SARS-CoV-2 infection may lead to esophageal mucosal injury, with acute esophagus necrosis (AEN) occurring in critically ill patients.[12] Two case reports have shown esophageal bleeding and multiple round herpetic-like erosions and ulcers by endoscopy in patients with GI symptoms, and SARS-CoV-2 RNA was detected in these esophageal lesions.[12,13] At the autopsy, two necrotic ulcers were detected at the hypopharynx (**Fig. 1**A, B). Histopathology showed full-thickness inflammatory cell infiltration with thinning of the pharyngeal wall at the level of the ulcer center (**Fig. 1**C, D).[6] Meanwhile, in the presence of cells positive for SARS-CoV-2 spike protein subunit 1, histologic examination showed moderate lymphocytic infiltration in the esophageal mucosa (**Fig. 1**E–H),[6] consistent with the histopathological features of viral esophagitis.

Gastric and Intestinal Pathology

The incidence of GI symptoms in patients with COVID-19 is shown in **Table 1**.

The appearance of GI symptoms in patients with COVID-19 seems to indicate disease progression, as GI symptoms are more common in severe and critically ill patients, and are associated with an increased risk of adverse outcomes.[14–16] Interestingly, other case-control studies had previously shown that the presence of GI symptoms was associated with longer illness duration, a trend toward lower ICU admissions, and lower mortality,[17] and the presence of GI symptoms could predict reduced disease severity and mortality.[18] The presence of SARS-CoV-2 RNA in feces is related to GI symptoms. Fecal shedding of viral RNA suggests prolonged GI infection.[19] In addition, the virus may persist in the GI tract after it was cleared from the respiratory tract.[19]

A multicenter study showed that ulcers were the most common lesions observed in upper GI endoscopy in patients with COVID-19, with the lesions sometimes accompanied by active bleeding.[20] Bhayana and colleagues[21] retrospectively analyzed the abdominal imaging findings of 412 patients with COVID-19, and a variety of abnormalities were observed. Bowel-wall abnormalities were found on 13 computed tomography (CT) images (31%), which were associated with intensive care unit (ICU) admission. Pneumatosis or portal venous gas was observed in four abdominal CT images obtained in patients in the ICU. Unusual yellow discoloration of the bowel was observed in three cases and bowel infraction in two cases. Pathologic examinations revealed ischemic enteritis, with patchy necrosis and fibrin thrombi in arterioles.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Amarapurkar and colleagues[22] also reported a case of hemorrhagic enteritis associated with COVID-19. Histopathology revealed extensive transmural hemorrhages with many congested and dilated blood vessels, and fibrin thrombi were occasionally observed in capillaries.

The GI pathology of SARS-CoV-2 infection had been verified in autopsy and biopsy studies. Liu and colleagues[23] observed alternating segmental dilatations and stenoses of the small bowel at the autopsy of a patient with COVID-19, associated with SARS-CoV-2 replication in GI mucosa.[19,20] Another report described GI alterations in patients with COVID-19 as characterized by lymphoplasmacytic infiltration in the lamina propria of the GI tract.[19] Coagulative necrosis, micro-hemorrhages, microthrombi, and vascular congestion had been found in the colonic mucosa, suggesting ischemia is one mechanism of injury. Such lesions have been found to be positive for COVID-19 by immunohistochemistry.[20] Duodenitis may also occur in critically ill patients with COVID-19, with endoscopic manifestations of diffuse bleeding, mucosal edema, and severe inflammation with erosions. Intracytoplasmic and intranuclear inclusions consistent with a viral infection were identified in duodenal crypts.[24]

Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine type 2 (TMPRSS2) receptors for SARS-CoV-2, are expressed in GI mucosa.[25,26] Experimental studies have shown human gastric organoids are susceptible to SARS-CoV-2 infection.[27] In addition, as both ACE2 and TMPRSS2 are expressed in the enteric nervous system, gut sensory-motor functions may be affected in susceptible patients with COVID-19.[28]

Pancreatic Pathology

SARS-CoV-2 receptors, including ACE2, TMPRSS2, NRP1,[29,30] and TFRC,[29] are expressed at very low levels in pancreatic β-cells; studies showed SARS-CoV-2 tropism for β cells in vitro.[31] SARS-CoV-2 infection has been shown to suppress insulin secretion and injure β cells ex vivo, eventually causing pancreatic dysfunction,[31] which leads to infection-related diabetes.[32] Among patients hospitalized with COVID-19, the prevalence of acute pancreatitis is 0.27%. COVID-19-associated acute pancreatitis is more frequently associated with severe systemic disease and multi-organ complications.[33]

Liver Pathology

SARS-CoV-2 can cause hepatic injury via direct binding to ACE2 receptors in cholangiocytes and hepatocytes, antibody dependent enhancement of infection, systemic inflammatory response syndrome, inflammatory cytokine storms, ischemia/reperfusion injury, and adverse events due to drug therapy.[9,34–37]

Findings in autopsies or postmortem biopsies of patients with coronavirus disease-2019

The main liver findings in patients with COVID-19 are shown in **Table 2** and are illustrated in **Fig. 2**A–E. The most common histopathological changes associated with

Fig. 1. Macroscopic examination of fresh (*A*) and fixed (*B*) hypopharynx, with two necrotic ulcer (*white arrows* in A). (*C*) Histopathology of ulcer in hypopharynx. (*D*) Inflammatory infiltration of the muscle layer with necrosis and degeneration of the skeletal muscle fibers (*E–H*). Moderate lympho-monocytic infiltration in esophageal mucosa (*E*—anti-CD68; *F*—anti-CD3; *G*—anti-CD20; *H*—positive for SARS-CoV-2 spike subunit 1, *black arrows*). (Porzionato A, Stocco E, Emmi A, et al. Hypopharyngeal Ulcers in COVID-19: Histopathological and Virological Analyses - A Case Report. Frontiers in immunology. 2021;12:676828. https://doi.org/10.3389/fimmu.2021.676828)

Table 1
Incidence of gastrointestinal symptoms in patients with coronavirus disease-2019

Studies	Number of Patients, *n*	GI Symptoms, *n* (%)	Anorexia, *n* (%)	Nausea, *n* (%)	Vomiting, *n* (%)	Diarrhea, *n* (%)	Abdominal Pain, *n* (%)	Virus RNA in Stool (+),*n* (%)
Xiao et al,[19] 2020	73	NA	NA	NA	NA	NA	NA	39(53.4)
Nobel et al,[17] 2020	278	97(34.9)	NA	63(64.9)		56(57.7)	NA	NA
Luo et al,[68] 2020	1141	183(16.0)	180(98.4)	134(73.2)	119(65.0)	68(37.2)	45(24.6)	NA
Hunt et al,[33] 2021	206	48(23.3)	NA	NA	NA	67(32.5)	NA	NA
Cheung et al,[5] 2020	59	15(25.4)	NA	NA	1(6.7)	13(86.7)	7(46.7)	9(60.0)
Pan et al,[69] 2020	204	103(50.5)	81(78.6)	NA	4(3.9)	35(34.0)	2(1.9)	NA
Jin et al,[15] 2019	651	74(11.4)	NA	17(23.0)	18(24.3)	56(75.7)	NA	NA
Wang et al,[70] 2020	138	NA	NA	14(10.1)	5(3.6)	14(10.1)	3(2.2)	NA
Ferm et al,[71] 2020	892	219(24.6)	105(11.8)	148(16.6)	91(10.2)	177(19.8)	70(7.8)	NA

Abbreviation: NA, not available.

Table 2
Summary of main hepatic findings in patients with coronavirus disease-2019

Ref.	No. Cases	Specimen Type	Steatosis	Portal Inflammation	Lobular Inflammation	Congestion/ Sinusoidal Dilation	Lobular Necrosis	Cholestasis	Hepatocyte Apoptosis	Vascular Pathology and/or Thrombosis
Greuel et al,[40] 2021	6	Autopsies	2/6 (33.3%)	–	–	–	–	1/6 (16.7%)	–	–
Xu et al,[44] 2020	1	Postmortem biopsy	1/1 (100%)	1/1 (100%)	1/1 (100%)	–	–	–	–	–
Tian et al,[50] 2020	4	Postmortem biopsies	1/4 (25%)	–	1/4 (25%)	3/4 (75%)	1/4 (25%)	–	–	–
Wang et al,[8] 2020	2	Postmortem biopsies	2/2 (100%)	2/2 (100%)	1/2 (50%)	–	–	–	2/2 (100%)	–
Sonzogni et al,[45] 2020	48	Postmortem biopsies	26/48 (54.2%)	32/48 (66.7%)	24/48 (50%)	–	18/48 (37.5%)	–	–	48/48 (100%)
Cai et al,[9] 2020	1	Postmortem biopsy	1/1 (100%)	–	1/1 (100%)	–	–	–	–	–
McConnell et al,[54] 2021	43	Postmortem biopsies	20/43 (46.5%)	10/43 (23.3%)	–	42/43 (97.7%)	–	–	–	–
Beigmohammadi et al,[47] 2021	7	Postmortem biopsies	7/7 (100%)	7/7 (100%)	–	7/7 (100%)	1/7 (14.3%)	2/7 (28.6%)	–	–
Lagana et al,[46] 2020,	40	Autopsies	30/40 (75%)	20/40 (50%)	–	–	20/40 (50%)	15/40 (37.5%)	10/40 (25%)	6/40 (15%)
Yurdaisik et al,[49] 2021	7	Postmortem biopsies	4/7 (57.1%)	2/7 (28.6%)	5/7 (71.4%)	1/7 (14.3%)	6/7 (85.7%)	2/7 (28.6%)	–	1/7 (14.3%)
Ramos-Rincon et al,[52] 2022	5	Postmortem biopsies	1/2 (50%)	–	–	–	1/5 (20%)	1/5 (20%)	–	–
Barton et al,[41] 2020	2	Autopsies	1/2 (50%)	–	–	–	–	–	–	–

Zhao et al,[43] 2021	17	Autopsies	12/17 (70.6%)	8/17 (47.1%)	5/17 (29.4%)	–	2/17 (11.8%)	–	–	–
Bradley et al,[48] 2020	14	Autopsies	9/14 (64.3%)	4/14 (28.6%)	1/14 (7.1%)	11/14 (78.6%)	4/14 (28.6%)	–	–	–
Wang XX et al,[51] 2021	1	Postmortem biopsy	1/1 (100%)	–	1/1 (100%)	–	1/1 (100%)	1/1 (100%)	1/1 (100%)	–
Chornenkyy et al,[55] 2021	8	Autopsies	4/8 (50%)	7/8 (87.5%)	6/8 (75%)	6/8 (75%)	4/8 (50%)	1/8 (12.5%)	–	–
Falasca et al,[58] 2020	22	Autopsies	12/22 (54.5%)	–	11/22 (50%)	10/22 (45.5%)	–	–	–	–
Fassan et al,[56] 2021	25	Autopsies	9/25 (36%)	–	–	21/24 (87.5%)	2/25 (8%)	–	–	3/25 (12%)
	3	Liver biopsies	2/3 (66.7%)	2/3 (66.7%)	1/3 (33.3%)	–	1/3 (33.3%)	–	–	–
Fraga et al,[59] 2020	1	Liver biopsy	–	1/1 (100%)	–	–	–	–	1/1 (100%)	–
Fiel et al,[57] 2021	2	Liver biopsies	–	2/2 (100%)	1/2 (50%)	–	2/2 (100%)	–	1/2 (50%)	–

–, finding was not described or found.

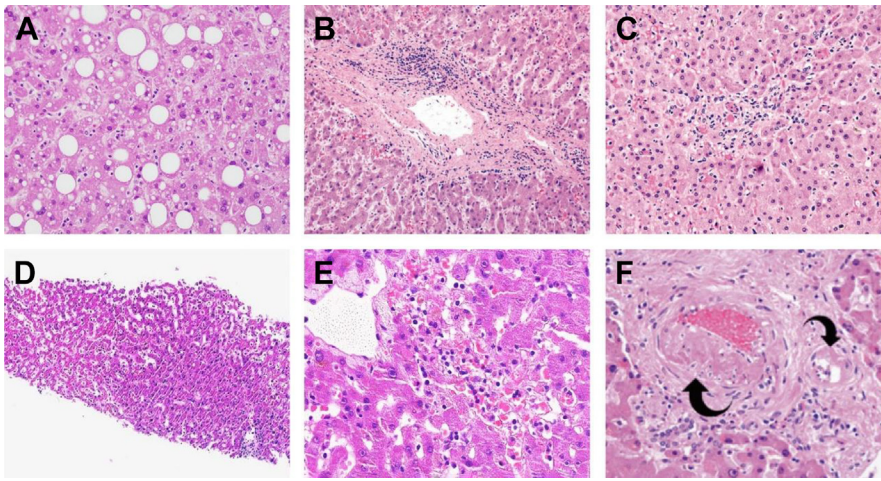

Fig. 2. Histology of liver changes in patients with COVID-19. (*A*) Steatosis. (*B*) Mild portal activity. (*C*) Mild lobular activity. (*D*) Mild sinusoidal dilatation with increased lymphocytic infiltration. (*E*) Focal centrilobular hepatic necrosis. (*F*) Portal arteriolar muscular hyperplasia (*left arrow*) and hyalinosis of a smaller branch of portal arteriole (*right arrow*). ([A] Zhao CL, Rapkiewicz A, Maghsoodi-Deerwester M, et al. Pathological findings in the postmortem liver of patients with coronavirus disease 2019 (COVID-19). Human pathology. Mar 2021;109:59-68. https://doi.org/10.1016/j.humpath.2020.11.015 (Ref. 43); [B, C] Chornenkyy Y, Mejia-Bautista M, Brucal M, et al. Liver Pathology and SARS-CoV-2 Detection in Formalin-Fixed Tissue of Patients With COVID-19. American journal of clinical pathology. May 18 2021;155(6):802-814. https://doi.org/10.1093/ajcp/aqab009 (Ref. 55); [D, E] Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. Jun 2020;33(6):1007-1014. https://doi.org/10.1038/s41379-020-0536-x (Ref. 50); [F] Lagana SM, Kudose S, Iuga AC, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. Nov 2020;33(11):2147-2155. https://doi.org/10.3389/fimmu.2021.676828)

SARS-CoV-2 are hepatic steatosis, mild lobular and portal inflammation, congestion/sinusoidal dilatation, lobular necrosis, and cholestasis.[38,39]

In several autopsy studies, hepatic steatosis of variable severity was the main findings,[40–42] which may be related to high BMI, as well as hypoxia and shock induced by COVID-19-related complications. It is well documented that shock and hypoxia can lead to lipid accumulation in hepatocytes and cause liver injury.[43] Postmortem liver biopsy examination carried out by Xu and colleagues[44] showed moderate microvesicular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury. In another study of 48 postmortem liver biopsies performed on patients with COVID-19, the histologic assessment also revealed microvesicular and macrovesicular steatosis (54%), mild portal inflammation (66%), and lobular inflammation (50%).[45] The same histologic findings were described in another study of 17 patients.[43] In a study of 40 autopsies, Lagana and colleagues[46] described gross findings of hepatic fibrosis in two patients. Histologically, macrovesicular steatosis was the most common finding, involving 30 patients (75%). Mild lobular necroinflammation and portal inflammation were present in 20 cases (50%) each.

In studies by Beigmohammadi and colleagues[47] and Bradley and colleagues,[48] congestion, steatosis and minimal-to-mild portal inflammation were the most common findings, whereas lobular inflammation was not prominent. Conversely, Yurdaisik and colleagues[49] observed lobular inflammation in most cases. Tian and colleagues[50] reported mild sinusoidal dilatation and focal macrovesicular steatosis in postmortem liver biopsies of four patients. There was mild lobular lymphocytic infiltration, which was insignificant in portal areas; the same findings were reported in another pathologic study.[9,51]

In addition, patchy hepatic necrosis has been described in postmortem liver biopsies and autopsies,[43,48–53] mainly in centrilobular areas (zone 3) and without evident inflammatory cellular infiltration. This pattern is consistent with acute ischemic injury. More severe changes such as confluent necrosis[45,47] and coagulative necrosis[51] were observed in rare cases.

Other histopathological changes frequently described in patients with COVID-19 include the proliferation of the intrahepatic bile ducts and the presence of intracanalicular bile plugs, consistent with cholestasis.[40,49,51–53] In fact, 38% of patients were shown to have lobular cholestasis among 40 autopsied cases, which were generally mild and focal.[46] Four (10%) of these patients had ductular cholestasis.[46] However, bile duct injury has not been observed.[43]

In postmortem wedge liver biopsies of 48 patients, Sonzogni and colleagues[45] noted alterations of vascular structures, both acute (thrombosis of portal and sinusoidal vessels, luminal ectasia) and chronic (fibrous thickening of vascular wall or phlebosclerosis, and abnormalities of the portal intrahepatic vasculature). Lagana and colleagues[46] reported similar changes, such as phlebosclerosis and sinusoidal microthrombi in six cases (15%).[43] Portal arterioles were abnormal (**Fig. 2**F) in nine cases (22.5%), including arteriolar muscular hyperplasia, hyalinosis of the vessel wall, and fibrinoid necrosis with endothelial apoptosis. These findings strongly suggest marked derangement of the intrahepatic blood vessel network secondary to systemic changes induced by the viral infection.

Other uncommon histologic changes include histiocytic hyperplasia in the portal tract,[43] platelet-fibrin microthrombi in the hepatic sinusoids, central vein, or portal vein, and rare megakaryocytes in sinusoids.[43] Minor to massive hepatocytic apoptosis,[8,51] and mild ballooning degeneration[9,40,46,47,54] have been described as well. Presence of SARS- CoV-2 in hepatocytes has been confirmed by in situ hybridization or RT-PCR.[45,46,50,52,55–57]

Liver pathology of patients with coronavirus disease-2019 in controlled studies

To further delineate the role of pre-existing conditions, Falasca and colleagues[58] showed in 22 COVID-19 autopsies (18 with comorbidities and 4 without comorbidities), that the incidence of macroscopic parenchyma congestion, histologic sinusoidal congestion, steatosis, and inflammatory infiltrate were similar between the two groups.[58]

In another postmortem study, patients with COVID-19 ($n = 8$) were compared with controls ($n = 4$). Minimal to focal mild portal tract chronic inflammation ($P < 0.05$) and mild focal lobular activity ($P = 0.06$) were more frequently observed in COVID patients.[46]

McConnell and colleagues[54] compared postmortem liver biopsies between 43 patients with COVID-19 versus normal controls ($n = 12$). Dilated sinusoids with congestion ($P < 0.01$), lobular inflammation ($P < 0.01$), steatosis ($P = 0.02$), and sinusoidal erythrocyte aggregation ($P < 0.01$) were more frequently observed in patients with COVID-19.

Pathology of liver biopsies in living patients with coronavirus disease-2019

Although findings at autopsy are often "contaminated" by terminal iatrogenic changes, liver biopsies performed in patient's premortem likely present more specific pathologic findings. Such findings include mild portal inflammation, scattered hepatocyte apoptosis, ground-glass hepatocytes consistent with cytoplasmic accumulation of fibrinogen,[59] activation of Kupffer cells, and steatosis.[56] In another study of 2 patients without significant lung disease, acute hepatitis, prominent bile duct damage, foci of centrilobular necrosis, and endothelitis were identified, although some of these changes may be due to post-transplant changes in one of the patients.[57]

Liver pathology in patients with underlying chronic liver diseases

Overall, 2% to 11% of patients with COVID-19 had underlying chronic liver disease.[37] Fatty liver disease or non-alcoholic steatohepatitis accounted for 42% of COVID-19 patients with preexisting liver diseases.[60] Hepatic dysfunction was significantly higher in patients with preexisting liver disease, especially in patients with cirrhosis and this was associated with poor outcomes.[60]

In a study of 202 consecutive patients with COVID-19,[61] patients with NAFLD had a higher risk of disease progression ($P < 0.0001$) and longer viral shedding ($P < 0.0001$) than those without NAFLD. Postmortem liver biopsies in one of these patients showed microvesicular steatosis with overactivation of T cells. However, other autopsy and biopsy studies only showed histologic findings consistent with shock liver[62] or the preexisting liver disease.[50]

Liver pathology in patients after vaccination

Hepatitis has been observed in some individuals after vaccination, that share some histologic features with autoimmune liver disease[63,64]; some contain diffusely distributed highly activated T cells.[65] Moreover, among the infiltrating T cells, there is an enrichment of T cells that are reactive to SARS-CoV-2, suggesting that the vaccine-induced cells can contribute to hepatic inflammation. In a cohort of 16 patients who presented with hepatic dysfunction after vaccination, 10 underwent liver biopsy. All showed portal inflammation (60% of which was graded as moderate or severe).[66]

In a case report of an 86-year-old man who died of acute renal and respiratory failure after receiving the first dose of the BNT162b2 mRNA COVID-19 vaccine, the autopsy showed stenosis and sinus dilatation in the liver.[67]

In summary, the most common histologic changes associated with SARS-CoV-2 in the liver are steatosis, mild lobular and portal hepatitis, congestion with sinusoidal dilatation, lobular necrosis, and cholestasis. Hepatocyte apoptosis, vascular pathology with or without thrombosis, histiocytic hyperplasia, and Kupffer cells hyperplasia may also occur.

CLINICS CARE POINTS

- GI symtoms due to involvement by COVID-19 are non-specific. Diagnosis may be facilitated by exclusion of other etiology and positive COVID test.
- Pathologically GI involvement is mainly characterized by lymphocytic infiltration of the mucosa.
- In patients with hepatic involvement, non-specific portal and/or lobular lymphocytic infiltration, mild steatosis, and rarely, spotty necrosis may be pathologic findings.

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